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MR Spectroscopy Shows Long Propylene Glycol Half-Life in Neonatal Brain

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Keywords
Neonate · Propylene glycol · MR spectroscopy · Half-life

Abstract
Introduction: Neonatal propylene glycol (PG) clearance is low with long plasma half-life. We hypothesized that neonatal brain PG clearance is diminished and may be related to perinatal asphyxia, infection, or stroke, via different blood-brain barrier permeability. This study aimed to estimate cerebral PG half-life with a clearance model including PG measured with MR spectroscopy (MRS) in neonates that received phenobarbital as the only PG source and to evaluate whether PG clearance was related to intracerebral pathology, for example, perinatal asphyxia, infection, or stroke. ***Methods:*** In this retrospective cohort study, 45 neonates receiving any dose of phenobarbital underwent MRS (short echo time single-voxel MRS at 1.5 T). Cumulative phenobarbital/PG doses were calculated. MRS indications were perinatal asphyxia (n = 22), infection (n = 4), stroke (n = 10), metabolic disease (n = 4), and others (n = 5). ***Results:*** Medians (interquartile range) included gestational age 39.4 (3.1) weeks, birth weight 3,146 (1,340) g, and cumulative PG dose 700 (1,120) mg/kg. First-order kinetics with mono-exponential decay showed cerebral PG half-life of 40.7 h and volume of distribution of 1.6 L/kg. Zero-order kinetics showed a rate constant of 0.048 mM/h and a volume of distribution of 2.3 L/kg, but the fit had larger residuals than the first-order model. There were no differences in ΔPG (i.e., PG estimated with clearance model minus PG observed with MRS) in infants with perinatal asphyxia, infection, or stroke. ***Discussion/Conclusion:*** This study showed a long cerebral PG half-life of 40.7 h in neonates, unrelated to perinatal asphyxia, infection, or stroke. These findings should increase awareness of possible toxic PG concentrations in neonatal brain due to intravenous PG-containing drugs.

Introduction

Propylene glycol (PG) improves drug solubility and stability, also for intravenous phenobarbital used neonatally. Hepatic alcohol dehydrogenase metabolizes PG to

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lactate and pyruvate; PG is eliminated renally [1, 2] (Fig. 1). PG clearance is saturable with non-linear pharmacokinetics after adult high doses [1]; however, lower neonatal concentrations show first-order kinetics with dose-dependent elimination [3]. Neonates have low PG clearance due to immature hepatic and renal function compared to adults [3–5]. In neonates, plasma PG half-life varies between 10.8 and 30.5 h [3, 6]. Consequently, neonates are at risk of PG accumulation and toxicity. Furthermore, with fast passive diffusion via the blood-brain barrier (BBB), long neonatal PG plasma half-life promotes cerebral accumulation and potential toxicity.

PG is generally regarded as safe [7]; the neonatal safety threshold is 1 mg/kg/day [8]. Daily PG doses exceeding safety thresholds are regularly administered to hospitalized neonates via PG-containing drugs [4, 5, 9, 10]. We demonstrated previously that administration of different pharmaceutical formulations with cumulative phenobarbital doses up to 40 mg/kg results in median cumulative PG doses up to 1,400 mg/kg [10]. This exceeds recommended safety thresholds [7, 8] and doses for which no short-term adverse effects were observed [9]. Short-term adverse PG effects include lactic acidosis, convulsions, haemolysis, and renal, hepatic, cardiac, or respiratory failure [6, 8, 11]; long-term adverse effects are largely unknown. Furthermore, high cumulative PG doses cause high brain PG concentrations on MR spectroscopy (MRS), affected by dose-to-MRS interval [10].

The BBB encompasses the microvascular endothelium with highly restrictive tight junctions between blood, cerebrospinal fluid (CSF), and the brain [12–14]. Neonatal BBB disruption can be caused by various pathological conditions, including perinatal asphyxia [12, 14], infection [13], and stroke [15], possibly leading to higher cerebral concentrations of potentially toxic molecules [14].

In this study, we estimated cerebral PG half-life based on MRS-detected PG in neonates that received phenobarbital, as the only PG source. We evaluated whether cerebral PG half-life was related to underlying diagnosis with possibly different BBB permeability.

Materials and Methods

Subjects

This retrospective cohort study included neonates born at 24–42 weeks gestational age in our neonatal intensive care unit between January 2016 and January 2019, as described previously [10], but amended with prolonged inclusion. In short, neonates were included if cerebral MRI/MRS at 1.5 T was performed between birth and 4 weeks after term equivalent age. Seventy-two infants were eligible for inclusion. Six infants with MRI at 3 T and 3 with insufficient MRS quality (movement artefacts) were excluded. Consequently, the original cohort included 63 neonates. The present study included 45 neonates receiving any dose of phenobarbital (sole PG source). The online supplementary material (see www.karger.com/doi/10.1159/000519282 for all online suppl. material) includes a STROBE checklist.

MRI/MRS indications were perinatal asphyxia (n = 22); infection (n = 4); stroke (n = 10); metabolic disease (n = 4), including hypoglycaemia (n = 3) and hyperammonaemia (n = 1); and other diagnoses (n = 5), including SCN2A mutation epilepsy (n = 2), hemimegalencephaly (n = 1), intoxication (n = 1), and 5th-day-fits (n = 1). Perinatal asphyxia was defined as ≥1 of the following: Apgar score ≤5 at 5 min; cardiopulmonary resuscitation; postnatal mechanical ventilation >10 min; or pH <7.10, base excess < −16 mmol/L, or lactate >10 mmol/L in the first postnatal hour. Perinatal infection included proven sepsis (i.e., positive blood culture) or clinical sepsis (i.e., clinical symptoms, elevated infection parameters, antibiotics, and negative blood culture) [16]. Perinatal stroke was MRI-diagnosed. Metabolic disease was diagnosed with specific biochemical characteristics.

Birth and phenobarbital dosing data were retrospectively collected from medical records. Birth data included gestational age (weeks), birth weight (g), mortality, and sex. Phenobarbital dosing data included time of administration, dosage (mg/kg), and injection solution, that is, 50 mg/mL (TEVA Pharmachemie, Haarlem, the Netherlands), 25 mg/mL (Apotheek A15, Gorinchem, the Netherlands), or 10 mg/mL phenobarbital (hospital pharmacy of Haarlem and Eindhoven, the Netherlands). All solutions contained 350 mg/mL PG and 336, 240, 329, and 237 mg/mL ethanol, respectively. Based on the phenobarbital dosages, the cumulative phenobarbital and PG dose (mg/kg) administered before MRS was calculated. Phenobarbital dose-to-MRS intervals (h) and postnatal age at MRS (h) were determined.

MRS Acquisition and Analysis

During MRI, neonates were placed on a special cushion for adequate positioning and preventing movements. Most infants were mechanically ventilated and intravenously received pain relief with morphine and/or sedation with midazolam, without PG, ethanol, or other alcohol-based excipients. In some infants, midazolam was anticonvulsive. Infants without mechanical ventilation were fed prior to MRI and not sedated.

Clinical conventional MRI was performed at 1.5 T (Avanto, Siemens, Erlangen, Germany) using an 8-channel head coil [10]. ^{1}H-MRS was performed with point-resolved spectroscopy localization at the right basal ganglia and thalamus with 14 mL volume of interest (VOI; 20 × 35 × 20 mm RL-AP-SI) [10]. Five subjects had slightly smaller VOI (8–12 mL); 4 subjects had VOI accidentally selected in the parietal cortex (8 mL [n = 3], 27 mL [n = 1]) – these spectra were included. The repetition time was 3,000 ms, echo time 30 ms, and 32 averages (64 averages in 4 subjects). Metabolite concentrations in millimolar (i.e., mmol/L VOI) were calculated with LCModel [17], using a standard basis set including lactate and additional model spectra of PG [18], pyruvate, ethanol, and simulating macromolecular and lipid signals. Quality parameters included spectral linewidth (full-width-at-half-maximum [Hz]) and signal-to-noise ratio (SNR), as normalized SNR corresponding to the standard protocol of VOI 14 mL and 32 averages.

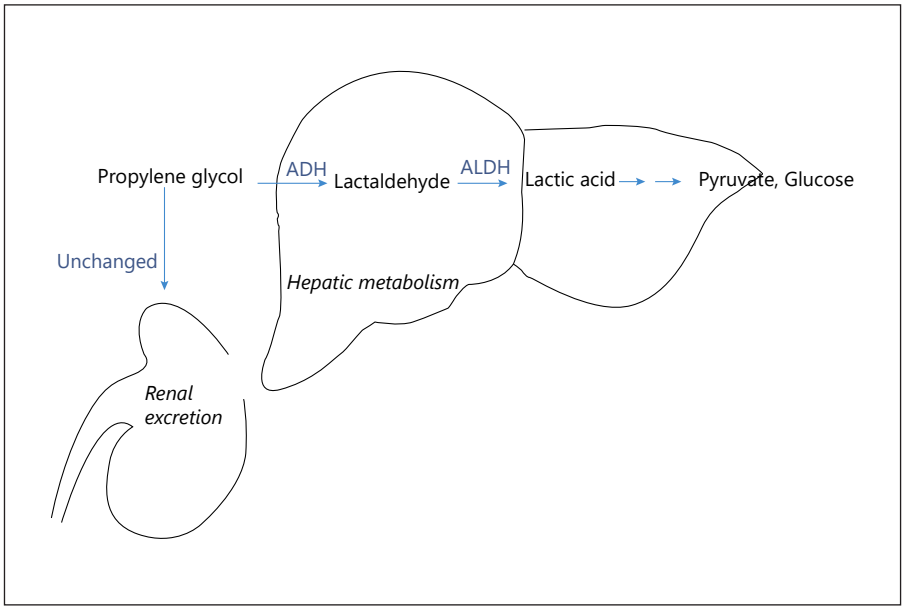

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Fig. 1. Propylene glycol metabolism in humans. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase.

Cerebral PG Clearance Model

We expressed estimated cerebral PG concentration as a function of PG dose and dose-to-MRS interval, assuming the same values for half-life and volume of distribution for all subjects. Based on PG dosages PG_i (mmol/kg) and administration-to-MRS interval Δt_i, we assumed first-order kinetics:

$$PG_{estimated} = \sum_i PG_i / V_d \times \exp\left(-\Delta ti / t_{1/2}\right).$$

First-order model: PG half-life $t_{½}$ (h) and volume of distribution *Vd* (L/kg brain tissue) were estimated by means of least squares optimization between $PG_{estimated}$ and $PG_{observed}$ (i.e., measured with MRS). Based on this clearance model, $PG_{predicted}$ was calculated per participant.

Zero-order kinetics is described in adults [1] and suggested for high neonatal PG dosages [3, 19]. Therefore, also a zero-order kinetics model was analysed, assuming the same values for the zero-order rate constant *k* and volume of distribution *Vd* for all subjects:

Zero-order model:

$$PG_{estimated} = \sum_i \left(PG_i / V_d - k\Delta t_{i,i+1}\right).$$

$\Delta t_{i,i+1}$: interval between subsequent phenobarbital/PG administrations (in case of multiple doses), and for the final dose the dose-to-MRS interval. In this equation, $PG_{estimated}$ cannot become negative. Parameters *k* and *Vd* were estimated by means of least squares optimization between $PG_{estimated}$ and $PG_{observed}$. To estimate whether PG kinetics is influenced by diagnosis, we compared ΔPG (differences between $PG_{predicted}$ [i.e., with PG clearance model] and $PG_{observed}$ [i.e., with MRS]) between diagnoses.

Statistics

Categorical variables were reported as frequencies (%) and analysed using χ^2 tests. Continuous variables were skewed and reported as median (interquartile range) and analysed using Mann-Whitney-U and Kruskal-Wallis tests. Normally distributed SNR was reported as mean ± SD and analysed using ANOVA. All analyses included post hoc Bonferroni correction for multiple testing. As lactate is a PG metabolite (Fig. 1), it was evaluated whether lactate and PG measured with MRS were correlated using Spearman's rho. All analyses were performed using IBM SPSS Statistics version 26. A p value < 0.05 was considered significant.

Table 1. Demographics and clinical data of the study population

Population characteristics	*n* = 45
Male, *n* (%)	26 (58)
Mortality, *n* (%)	13 (29)
Postnatal age at death, h	182 (166)
Gestational age, weeks	39.4 (3.1)
Birth weight, g	3,146 (853)
Phenobarbital administration[a]	
Phenobarbital total dose, mg/kg	40 (20)
PG total dose, mg/kg	700 (1,120)
Interval last dose phenobarbital to MRI, h	29.2 (80.7)
Cerebral MRS	
Postnatal age at MRS, h	104 (64)
Postmenstrual age at MRS, weeks	40.4 (3.1)
SNR	15.9±4.2
FWHM, Hz	1.5 (0.51)
MRS PG, mM	1.7 (3.9)
MRS lactate, mM	0.8 (0.7)

Parameters are reported as frequencies (%), median (IQR), or mean ± SD. FWHM, full-width at half-maximum; MRS, MR spectroscopy; PG, propylene glycol; SNR, signal-to-noise ratio; SD, standard deviation; IQR, interquartile range. [a] Phenobarbital was the only medication containing PG (all formulations contained 350 mg/mL PG).

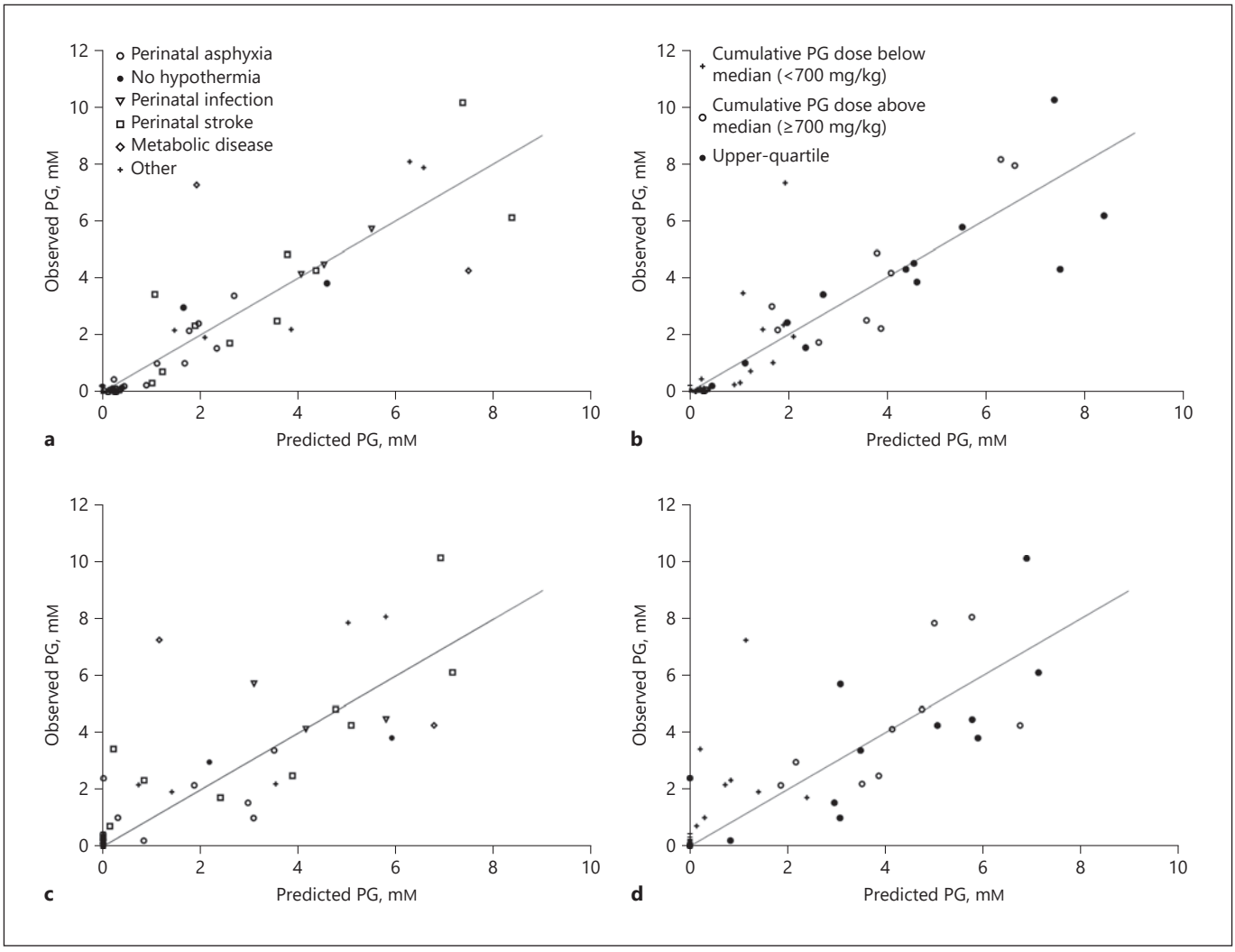

Fig. 2. PG clearance model. First-order model: $PG_{observed}$ measured with MRS versus $PG_{predicted}$ based on least-squares optimization estimated a PG half-life of 40.7 h and a volume of distribution of 1.6 L/kg (n = 45) classified by diagnosis (**a**); classified by cumulative PG dose above and below the median (i.e., 700 mg/kg) (**b**). Zero-order model: $PG_{observed}$ measured with MRS versus $PG_{predicted}$ based on least-squares optimization estimated a PG rate constant of elimination of 0.048 mM/h and a volume of distribution of 2.35 L/kg (n = 45) classified by diagnosis (**c**); classified by cumulative PG dose above and below the median (i.e., 700 mg/kg) (**d**). Line of identity was plotted in (**a**–**d**). MRS, MR spectroscopy; PG, propylene glycol.

Results

Subjects

The gestational age was 39.4 (3.1) weeks, birth weight 3,146 (853) g, and chronological age at MRI/MRS 104 (64) h (Table 1). After the first phenobarbital dose (20 mg/kg according to national guidelines), 33 neonates received a second (10 mg/kg), 21 a third (10 mg/kg), and 3 a fourth dose (10 mg/kg). Neonates received different phenobarbital formulations: 10 mg/mL (n = 20), 25 mg/mL (n = 11), 50 mg/mL (n = 8), or combinations (n = 6). Administration of 10 mg/mL phenobarbital resulted in higher cumulative PG dose (1,400 [431] mg/kg) than 25 mg/mL (426 [288] mg/kg) and 50 mg/mL (210 [140] mg/kg) ($p < 0.001$). Different phenobarbital formulations had similar lactate on MRS.

With regard to MRS, $PG_{observed}$ was not correlated with its metabolite lactate (Spearman's rho 0.18, p = 0.2). Neither ethanol nor pyruvate was detected on MRS, indicating their concentrations were below detection level, that is, well below approximately 0.1–0.2 mM (considering high neonatal spectral quality).

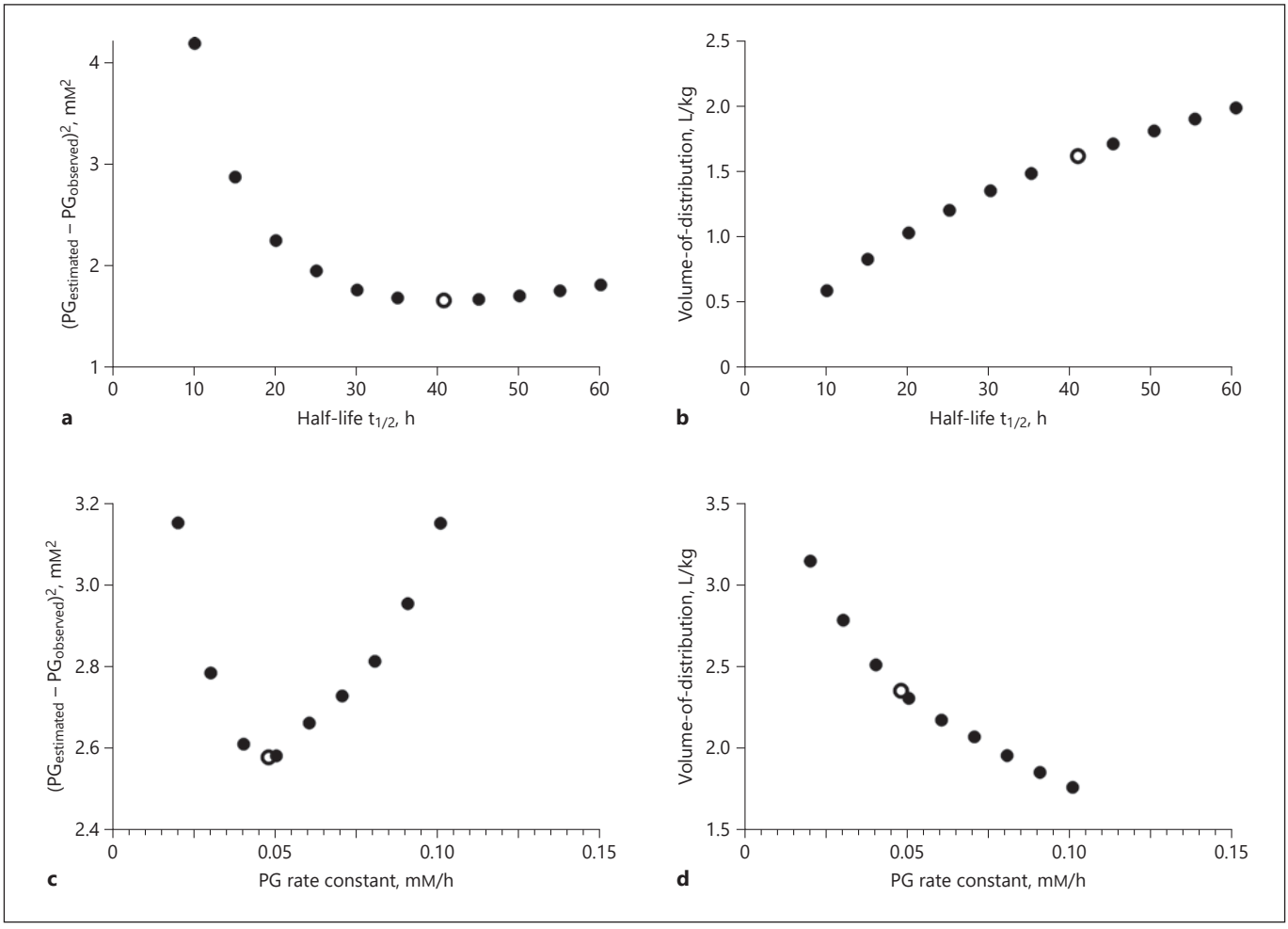

Fig. 3. Goodness of fit of PG clearance model. First-order model: squared difference between $PG_{estimated}$ and $PG_{observed}$, that is, $(PG_{estimated} - PG_{observed})^2$, versus half-life illustrating a broad minimum (**a**); corresponding volume of distribution versus PG half-life ($t_{½}$) (**b**). Open dots illustrate a half-life of 40.7 h and a volume of distribution of 1.6 L/kg, leading to minimum $(PG_{estimated} - PG_{observed})^2$. Zero-order model: squared difference between $PG_{estimated}$ and $PG_{observed}$, that is, $(PG_{estimated} - PG_{observed})^2$, versus PG rate constant illustrating a steep minimum (**c**); corresponding volume of distribution versus PG rate constant (**d**). Open dots illustrate a PG rate constant of 0.048 mM/h and a volume of distribution of 2.35 L/kg, leading to minimum $(PG_{estimated} - PG_{observed})^2$. PG, propylene glycol.

Cerebral PG Clearance Model

First-order kinetics resulted in a PG half-life of 40.7 h and volume of distribution of 1.6 L/kg (Fig. 2a). Cumulative PG doses above or below the median were similarly distributed over the fit (Fig. 2b). The average squared difference between $PG_{estimated}$ and $PG_{observed}$ showed a flat minimum of 1.66 mM^2 (Fig. 3a). When assuming lower half-life, the estimated volume of distribution becomes smaller (Fig. 3b) at the cost of an increased squared difference.

Zero-order kinetics showed a rate constant k of 0.048 mM/h and a volume of distribution of 2.35 L/kg (Fig. 2c). Cumulative PG doses above or below the median were similarly distributed over the fit (Fig. 2d). The minimum average squared difference between $PG_{estimated}$ and $PG_{observed}$ of 2.58 mM^2 for this model was clearly higher than for first-order kinetics, making the first-order model superior (Fig. 3c, d).

Clinical Diagnosis

Four of the 22 asphyxiated neonates did not receive therapeutic hypothermia, due to prematurity (n = 1) or lack of encephalopathy (n = 3). Asphyxiated neonates with and without therapeutic hypothermia did not differ, except for higher postnatal age at MRS in those with hy-

Table 2. Demographics and clinical data by diagnosis

Population characteristics	Perinatal asphyxia (n = 22)	Perinatal infection (n = 4)	Perinatal stroke (n = 10)	Metabolic disease (n = 4)	Other diseases (n = 5)
Mortality[a], *n*, %	8 (36)	1 (25)	2 (20)	1 (25)	1 (20)
Gestational age, weeks	40.6 (2.7)	39.6 (4.0)	39.6 (3.7)	38.1 (2.3)	38.0 (3.9)
Birth weight, g	3,168 (772)	3,350 (1,077)	3,102 (994)	3,545 (1,439)	2,854 (1,099)
Cumulative dose					
Phenobarbital, mg/kg	35 (20)	40 (9.4)	40 (2.7)	35.5 (17)	30 (15)
PG, mg/kg	646 (1,138)	1,260 (398)	840 (1,120)	493 (874)	840 (735)
Cerebral MRI/MRS					
Postnatal age at MRS, h	113.5 (26.3)[1]	105 (352.5)	42 (39.3)	295 (458.6)	30 (–)
SNR	16.4 (4.3)	14.3 (3.6)	15.8 (4.5)	13.5 (3.9)	17.4 (4.4)
FWHM, Hz	1.7 (1.1)	1.7 (4.5)	1.5 (1.1)	1.2 (0.9)	2.0 (0.5)
MRS PG, mM	0.2 (1.6)[2]	4.3 (4.4)	3.0 (3.7)	2.3 (6.5)	2.2 (5.9)
MRS lactate, mM	0.85 (1.1)	0.9 (1.5)	0.7 (1.2)	1.2 (0.8)	0.6 (0.3)
ΔPG[b], mM	−0.1 (0.4)	0.01 (0.4)	−0.3 (2.3)	0.1 (6.5)	0.7 (2.5)

Between-group comparisons by the Kruskal-Wallis test and Bonferroni correction for multiple testing. Parameters are reported as median (IQR), except for mortality as frequency (%) and SNR as mean ± SD. FWHM, full-width at half-maximum; MRS, MR spectroscopy; PG, propylene glycol; SNR, signal-to-noise ratio; SD, standard deviation. [a] Median postnatal age at death: asphyxia 188 h and stroke 90 h. [b] ΔPG = $PG_{predicted}$ (i.e., by PG clearance model) – $PG_{observed}$ (i.e., measured with MRS). [1] Perinatal asphyxia versus perinatal stroke, $p < 0.006$. [2] Perinatal asphyxia versus perinatal stroke, $p = 0.02$.

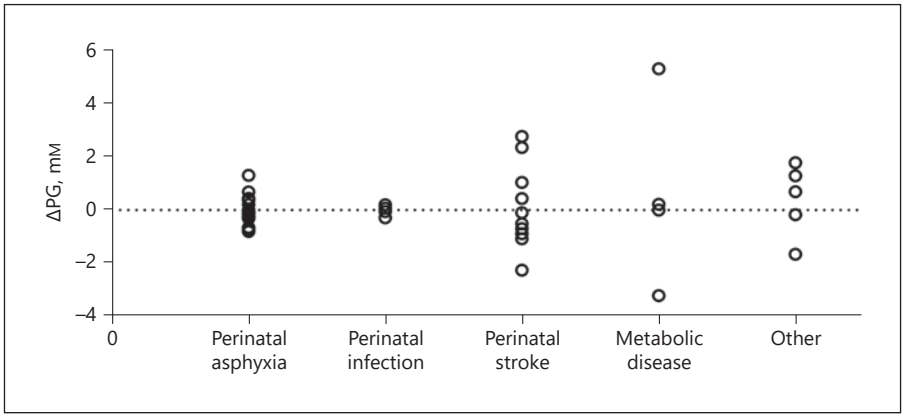

Fig. 4. ΔPG by diagnosis. ΔPG, cerebral $PG_{predicted}$ (i.e., by PG first-order clearance model) – cerebral $PG_{observed}$ (i.e., measured with MRS). No significant differences between groups. PG, propylene glycol; MRS, MR spectroscopy.

pothermia as MRI/MRS was performed after normothermia restoration (online suppl. Table). In other groups, some neonates fulfilled perinatal asphyxia criteria, that is, Apgar score ≤5 or biochemical criteria (infection n = 2; stroke n = 2; metabolic disease n = 1; other n = 1); none were eligible for therapeutic hypothermia.

Population characteristics, spectral quality parameters, and MRS lactate were not different between diagnoses (Table 2). $PG_{observed}$ was lower in neonates with perinatal asphyxia versus stroke. Due to hypothermia-related delay, neonates with perinatal asphyxia had higher postnatal age at MRS particularly than stroke (Table 2; online suppl. Figure).

With first-order kinetics, ΔPG (i.e., $PG_{predicted}$ – $PG_{observed}$) was not different between groups (Table 2; Fig. 4). In asphyxiated neonates, ΔPG was not different between those with and without therapeutic hypothermia (online suppl. Table).

Discussion/Conclusion

This study demonstrated a long PG half-life of 40.7 h in neonatal brains. Assuming fast BBB diffusion, plasma half-life may also be longer than previously reported, 10.8–30.5 h [3, 6]. Diminished hepatic and renal clear-

ance result in long neonatal plasma PG half-life compared to children and adults [3–5]. In our study, phenobarbital administration caused cerebral PG. Neonates received a median cumulative PG dose of 700 mg/kg [10], far exceeding the neonatal safety threshold of 1 mg/kg/day [8]. Combined with long cerebral PG half-life, neonates may have short-term [6, 8, 11] and possible long-term adverse effects, which, to date, are not clearly defined in humans. High/repeated PG exposure results in cerebral apoptosis in mice and may result in short-term brain disturbances in infants [20]. However, it remains unknown if this results in long-term cognitive/behavioural abnormalities [20].

Neonatal brain PG concentrations might relate to changed BBB permeability due to perinatal asphyxia [12, 14], infection [13], or stroke [15], influencing passive BBB passage of PG. Hypoxia-ischemia causes endothelial injury, systemic inflammation, and reperfusion, increasing BBB permeability [12, 14, 15]. We showed similar PG clearance in asphyxia with or without therapeutic hypothermia, although differences cannot be excluded as groups were small. However, hypothermia does not affect phenobarbital clearance, after accounting for weight and postconceptional age [21, 22]. More data are needed to evaluate if hypothermia influences cerebral PG clearance. Cerebral infection upregulates transcription factors that downregulate and remodel tight junctions, resulting in increased BBB permeability [13]. We demonstrated similar ΔPG in neonates with perinatal asphyxia, infection, stroke, and metabolic disease, although we noticed large inter-subject variation in neonates with stroke and metabolic disease and the subgroups were small. Based on these indirect findings, we speculate that PG brain penetrance and clearance might not be related to BBB disruption. However, we cannot exclude certain conditions resulting in cerebral PG retainment. In addition, we assumed that PG_{observed} is representative for actual cerebral concentrations. Although PG detection by 1H-MRS is correlated with CSF-PG [23], no gold standard is available. We cannot relate PG_{observed} with plasma concentrations as these were unavailable.

Hepatic PG degradation results in lactate and pyruvate [1, 2]. In our study, MRS lactate did not correlate with $PG_{observed}$ and lactate was not different between groups (Table 2). These findings may, among others, be influenced by postnatal age at MRS. Also, we hypothesize that other reasons of lactate production are possible, for example, tissue hypoxia, inflammation, or metabolic. Moreover, PG degradation to lactate is hepatic and not cerebral; high serum lactate may not result in cerebral lactate. We did not detect pyruvate on MRS. Also, ethanol, another solvent of phenobarbital, was not detected. Ethanol is eliminated before PG via the same alcohol dehydrogenase pathway (Fig. 1). Thus, ethanol might be missed because MRS was not obtained shortly after phenobarbital administration. Furthermore, we may assume that PG half-life may be shorter, in the absence of ethanol. However, co-administration of PG and ethanol is common.

This study was the first to describe a cerebral PG clearance model, similar to plasma [3]. All neonates followed a consistent MRI/MRS protocol and received similar standard care. MR spectra had high quality without between-group quality differences.

There were several limitations. First, we acknowledge limitations of retrospective studies. A prospective design is expected to be ethically challenging. High PG doses were unexpected and ascribed to market withdrawal of phenobarbital formulation. Formulation options with regard to phenobarbital/PG concentrations were limited. Still, this study is important for awareness of high cerebral concentrations and diminished clearance after PG-containing drugs. Second, the retrospective design limited sample size and data availability. Consequently, power analysis was unavailable. Also, diagnoses were unequally distributed with small groups, influencing statistical possibilities. Several criteria defined perinatal asphyxia. Overlap of these criteria between diagnostic groups may increase similarity and decrease differences. Third, the PG clearance model assumed population-based kinetics independent of gestational age, body weight, and metabolism. Because almost all neonates were term-born, gestational age differences were small. We concluded that first-order kinetics were more appropriate to describe our study population than zero-order kinetics. Nonetheless, the role of zero-order kinetics in high PG doses cannot be excluded. Unfortunately, we cannot model combined first- and zero-order kinetics as consistent intra-individual longitudinal data and short dose-to-MRI intervals are lacking. Also, we only focused on PG clearance after phenobarbital administration and did not take possible competition between ethanol and PG into account, both alcohol dehydrogenase substrates [24]. PG half-life might be shorter in the absence of ethanol as excipient-excipient interaction is lacking. Thus, the current study's PG clearance is only valid for neonatal phenobarbital containing PG and ethanol. Lastly, the cerebral PG clearance model was not independently validated. Also, $PG_{observed}$ was not compared to serum-PG or CSF-PG as these were unavailable. Taken this into account, results need to be interpreted cautiously.

In conclusion, this MRS study showed a long neonatal cerebral PG half-life of 40.7 h based on first-order kinetics. Furthermore, PG clearance was similar in neonates with different diagnoses, but small groups should be accounted for. This might increase awareness of possible toxic neonatal cerebral PG concentrations due to intravenous PG-containing drugs. High PG administration should be avoided. MRS should be strongly considered when performing neonatal MRI with analysis including PG and ethanol in case of PG-containing drugs.

Future studies should compare neonatal brain and plasma PG, ethanol and lactate in asphyxia, stroke, and infection to make firmer statements about BBB changes possibly influencing cerebral PG exposure and toxicity. Furthermore, the clearance model we presented should be validated in neonatal controls. Also, intra-individual longitudinal data with different, including short, PG-dose-to-MRS intervals may elucidate the presence of zero-order kinetics after high neonatal PG dosages.

Statement of Ethics

As evaluated by the Medical Ethics Review Committee of Amsterdam UMC, Amsterdam, The Netherlands, the Medical Research Involving Human Subjects Act did not apply to this study; therefore, there was waiver of informed consent. Furthermore, the study is exempt from ethical committee approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Dr. van de Lagemaat and Dr. Pouwels conceptualized and designed the study, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. van de Pol, Dr. Zonnenberg, and Dr. Witjes conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Data Availability Statement

De-identified individual participant data will not be made available. Group data may be provided upon specific request.

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